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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/538,248	03/29/2000	David A. Cheresh	TSRI-651.3	6166

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/538,248	CHERESH ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see atached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *1-4,17-20,32 and 33*.

   Claim(s) withdrawn from consideration: *none*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Rebecca E. Prouty
Primary Examiner
Art Unit: 1652

The rejection of Claims 1, 2, 17, and 18 under 35 U.S.C. 102(e) as being anticipated by Calderwood et al. (US Patent 6,001,839) is maintained.

Applicants argue that the Calderwood et al. patent teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema but does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivity and activity depending on the spatial arrangement of substituents. This is not persuasive because Calderwood et al. clearly teach the use of each of the specific compounds listed in columns 7-10 for the treatment of VEGF-mediated edema and as the patent teaches the specific structures of these compounds as well as methods of making them the methods disclosed are unquestionably enabled. This list includes the specific compounds 7-isopropyl-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, (column 9, lines 7-8), 5-[4-(4-aminophenoxy)phenyl]-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (column 9, lines 32-33), and 5-[4-(3-aminophenoxy)phenyl]-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (column 9, lines 34-35), which Burchat et al. (2000) evidence are src kinase inhibitors (see Table 2). Applicants statement that Burchat et al. does not show inhibition of c-src is not understood as Table 2 of Burchat et

al. is clearly an assay of the ability of the recited compounds to inhibit a variety of Src family members including src.

The rejection of Claims 1, 2, 17, and 18 under 35 U.S.C. 102(e) as being anticipated by Calderwood et al. (US Patent Application 2003/0187001) is maintained.

Applicants argue that the Calderwood et al. application teaches that certain pyrrolopyrimidine compounds are useful for treating VEGF mediated edema but does not teach or suggest that the pyrrolopyrimidine compounds are inhibitors of human c-src. The selectivity of tyrosine kinase inhibitors is highly unpredictable with large variability in selectivity and activity depending on the spatial arrangement of substituents. This is not persuasive because Calderwood et al. clearly teach the use of each of the specific compounds disclosed for the treatment of VEGF-mediated edema and as the application teaches the specific structures of these compounds as well as methods of making them the methods disclosed are unquestionably enabled. This specifically disclosed compounds include 4-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl Alcohol, (paragraph 0482), 2-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzyl Alcohol (paragraph 0495), 4-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile (paragraph 0439) and 2-[4-(4-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)phenoxy]benzonitrile (paragraph 0447), which Burchat et al. (2000) evidence are src

kinase inhibitors (see Table 2). Applicants statement that Burchat et al. does not show inhibition of c-src is not understood as Table 2 of Burchat et al. is clearly an assay of the ability of the recited compounds to inhibit a variety of Src family members including src.

The rejection of Claims 1, 2, 17, and 18 under 35 U.S.C. 102(e) as being anticipated by Hirst et al. (US Patent Application 2002/0156081) is maintained.

Applicants argue that Hirst et al does not provide an enabling disclosure of the presently claimed invention. Applicants argue that treatment of edema is discussed only generally in a laundry list of conditions in paragraph 315 of Hirst et al. and that the application states only that some of the compounds can be used to treat edema. Applicants argue that of the over 950 examples of compounds presented in Hirst et al. there is not a single data point of inhibition data. Only general allusions to unspecific activity against various diverse classes of tyrosine kinases is provided. This is not persuasive because despite the fact that treatment of edema is only one of several conditions to be treated Hirst et al. clearly teach the use of each of the 982 compounds of examples 1-982 for the treatment of edema and teach how to make each of these specific compounds and thus the methods disclosed are unquestionably enabled. As such the use of each of these compounds is clearly enabled by Hirst et al. The examples include the specific

compounds trans-Benzyl N-[4-[4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]carbamate (see paragraph 0686), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]benzamide (see paragraph 0697), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-2,2-dimethyl-3-phenylpropanamide (see paragraph 2549), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-3-methyl-3-phenylbutanamide (see paragraph 2562), trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]benzo[b]furan-2-carboxamide, (see paragraph 2585), Trans-3-[4-(Benzylamino)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine, (see paragraph 0929) and trans-N-[4-[4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl]-3-phenylpropanamide (see paragraph 1696) which Burchat et al. (2002) evidence are src kinase inhibitors (see Tables 3 and 4). Applicants statement that Burchat et al. (2002) has a date after the filing date of the present application and thus does not support the instant rejection is not persuasive. Burchat et al. (2002) was only used to evidence that the specific compounds disclosed by Hirst et al. inherently are Src kinase inhibitors. Use of a later filed disclosure to

show that a characteristic not disclosed in the reference is inherent in the prior art compound is proper (See MPEP 2131.01).

The rejection of Claims 3, 4, 19, 20, 32, and 33 under 35 U.S.C. 103(a) as being unpatentable over Calderwood et al (US Patent 6,001,839), Calderwood et al. (US Patent Application 2003/0187001) and Hirst et al. (US Patent Application 2002/0156081) in view of Hanke et al. is maintained.

Applicants response merely repeats word for word their previous traversal of the instant rejection which was addressed in the previous Office Action. As such this rejection is maintained for the reasons presented therein. Regarding claims 19, 20 and 32, and In re Ngai, 70 U.S.P.Q. 1862, applicants argue that Ngai is readily distinguishable. Applicants argue that the specific composition containing human c-src tyrosine kinase inhibitor and capable of modulating vascular permeability increase as defined by these claims is not in the prior art and neither is a packaged version of that composition as claimed. The argument is not understood. Hanke et al. unquestionably teaches compositions of PP1 and PP2. There is no difference between the compositions of PP1 and PP2 of Hanke et al. and those of the instant claims. Furthermore, the inclusion of a pharmaceutical composition in a package with printed material is well known in the art and does not define a patentable feature of the composition. What the printed matter states cannot

define the invention. While a new use for an old compound may be patentable the compound itself is not.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652